the goal for the claimed method which is stated in the preamble of claims 1 and 17. As noted, support for these amendments can be found in the preamble of claim 1 and, thus, no new matter has been introduced.

The Draftsperson has objected to the figures submitted with the original application for the reasons set forth in PTO FORM 948. Applicants respectfully request that the Draftsperson's objections to the figures be held in abeyance until issuance of a formal Notice of Allowance. At that time, Applicants will file formal drawings which will overcome the stated objections.

Claims 1-18 have been rejected under 35 U.S.C. § 112, first paragraph, for failing to provide an enabling disclosure. Claims 1-18 have been rejected under 35 U.S.C. § 112, second paragraph, as indefinite. Claims 1-16 have been rejected under 35 U.S.C. § 103 as being unpatentable over Fodor, *et al.* (WO/92/10588) in view of Sambrook, *et al.* (Molecular Cloning: A Laboratory Manual, Cold Springs Harbor Laboratory Press, Cold Spring Harbor, N.Y., p. 5.80, 7.58-7.78). Claims 17-18 have been rejected under 35 U.S.C. § 103 as being unpatentable over Fodor in view of Keith, *et al.* (U.S. Patent No. 5,093,245). For the reasons set forth herein, each of the Examiner's rejections is overcome.

THE INVENTION:

The present invention provides improved methods for discriminating between fully complementary hybrids and those that differ by one or more base pairs. In one embodiment, the present invention provides methods of using nuclease treatment to improve the quality of hybridization signals on high density oligonucleotide arrays. More particularly, in one such method, an array of oligonucleotides is combined with a labelled target nucleic acid to form target-oligonucleotide hybrid complexes. Thereafter, the target-oligonucleotide hybrid complexes are treated with a nuclease and, in turn, the array of target-oligonucleotide complexes are washed to remove non-perfectly complementary target-oligonucleotide hybrid complexes. Following nuclease treatment, the target:oligonucleotide hybrid complexes which are perfectly complementary are more readily identified. From the location of the labelled targets, the oligonucleotide probes which hybridized with the targets can be identified and, in turn, the sequence of the target nucleic acid can be more readily determined or verified.

In another embodiment, the present invention provides methods wherein ligation reactions are used to discriminate between fully complementary hybrids and those that differ by one or more base pairs. In one such method, an array of oligonucleotides is generated on a substrate (in the 3' to 5' direction) using any one of the methods described herein. Each of the oligonucleotides in the array is shorter in length than the target nucleic acid so that when hybridized to the target nucleic acid, the target nucleic acid generally has a 3' overhang. In this embodiment, the target nucleic acid is not necessarily labelled. After the array of oligonucleotides has been combined with the target nucleic acid to form target-oligonucleotide hybrid complexes, the target-oligonucleotide hybrid complexes are contacted with a ligase and a labelled, ligatable probe or, alternatively, with a pool of labelled, ligatable probes. The ligation reaction of the labelled, ligatable probes to the 5' end of the oligonucleotide probes on the substrate will occur, in the presence of the ligase, only when the target:oligonucleotide hybrid has formed with correct base-pairing near the 5' end of the oligonucleotide probe and where there is a suitable 3' overhang of the target nucleic acid to serve as a template for hybridization and ligation. After the ligation reaction, the substrate is washed (multiple times if necessary) with water at a temperature of about 40°C to 50°C to remove the unbound target nucleic acid and the labelled, unligated probes. Thereafter, a quantitative fluorescence image of the hybridization pattern is obtained by scanning the substrate with, for example, a confocal microscope, and labelled oligonucleotide probes, *i.e.*, the oligonucleotide probes which are perfectly complementary to the target nucleic acid, are identified. Using this information, the sequence of the target nucleic acid can be more readily determined or verified.

REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH:

Claims 1-18 have been rejected under 35 U.S.C. § 112, first paragraph, for failing to provide an enabling disclosure. In making this rejection, the Examiner has stated that the disclosure is enabling only for claims limited to target nucleic acids shorter than 22 nucleotides in length of the previously defined sequence.

Applicants disagree and, in doing so, they respectfully submit that the claims are fully enabled by the specification as filed. Using the teachings of the specification, one of ordinary skill in the art can readily determine or verify the sequence of ***any*** target nucleic

acid. A review of the specification reveals that Applicants have provided a very detailed teachings regarding the generation of an array of oligonucleotides, sequencing by hybridization, methods for enzymatic discrimination enhancement, detection methods, data analysis methods, *etc.* In view of the extensive teachings provided by Applicants, it is respectfully submitted that using the methods of the present invention, one of ordinary skill in the art would be able to sequence or resequence any target nucleic acid without "undue" experimentation.

It is well-settled that enablement is not precluded by the necessity for some experimentation. However, the experimentation needed to practice the invention must not be undue experimentation. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 U.S.P.Q. 81, 94 (Fed. Cir. 1986). "The key word is 'undue,' not 'experimentation.'" *In re Angstadt*, 190 U.S.P.Q. 214, 219 (C.C.P.A. 1976). As stated in *U.S. v. Telectronics, Inc.*, 8 U.S.P.Q. 1217 (Fed. Cir. 1988):

> The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. . . . A patent may be enabling even though some experimentation is necessary; the amount of experimentation, however, must not be unduly extensive.

Id. at 1222-1223.

Applicants respectfully submit that the specification provides a sufficient guide to enable the skillful artisan to make and/or use the claimed invention. Again, Applicants have provided a detailed accounting regarding generating an array of oligonucleotides, sequencing by hybridization, enzymatic discrimination enhancement, detection methods, data analysis, *etc.* Moreover, many different detection systems and methods for analyzing data are known to those of skill in the art. In fact, WO 92/10588, a reference which was cited by the Examiner in the obviousness rejection, provides numerous teachings regarding different methods which can be used for detection and data analysis. The teachings of WO/92/10588 were incorporated by reference into Applicants' specification as originally filed. As such, the specification provides a sufficient guide to enable the skillful artisan to make and/or use the claimed invention ***without undue experimentation***.

In addition to the foregoing, Applicants submit that they are somewhat puzzled as to how the Examiner determined that the claims are enabled for target nucleic acids "shorter than 22 nucleotides in length" (*see*, page 3 of the Office Action). It appears that the Examiner may have picked this number based on the length of the target nucleic acids used in the examples relating to enhanced discrimination using ligase reactions. However, in view of the extensive teachings provided by Applicants in the specification, it is improper for the Examiner to require that the claims be limited to the embodiments set forth in only a ***portion*** of the examples.

In fact, Applicants point out to the Examiner that in Example I of the section entitled "Enhanced Discrimination Using RNAse A," Applicants sequenced a 1.3kb region spanning the D-loop region of human mitochondrial DNA (mtDNA). This example unequivocally establishes that Applicants' methods can readily be used to sequence a target nucleic acid of a length which is over 59 times as long as the length suggested by the Examiner. In view of this example, Applicants do not understand why the length of the target nucleic acid should be limited to 22 nucleotides.

Again, in view of the broad teachings provided by Applicants, it is improper for the Examiner to require that the claims be limited to a particular embodiments set forth in the examples. Thus, Applicants respectfully submit that using the teachings of the specification, one of ordinary skill in the art would be able to sequence or resequence ***any*** target nucleic acid without "undue" experimentation.

In view of the foregoing amendments and remarks, Applicants respectfully submit that the § 112, first paragraph, concerns of the Examiner have been overcome. Accordingly, Applicants urge the Examiner to withdraw the rejection based on 35 U.S.C. § 112, first paragraph.

REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH:

Claims 1-18 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as their invention. Each of the Examiner's concerns and, in turn, Applicants' responses to those concerns are set forth herein.

a. The Examiner has questioned the use of the phrase "positionally distinguishable oligonucleotides each of which binds to a defined subsequence of preselected length" in claims 1 and 17. In doing so, the Examiner has raised some concern over the position of the oligonucleotides in the array and whether the oligonucleotides making up the array are all of the same sequence and length.

Applicants respectfully submit that those skilled in the art would clearly understand the meaning of this phrase when read either alone or in view of the teachings of the specification and, thus, it is not vague or indefinite. More particularly, as explained in the specification, the methods of the present invention rely, in part, on the ability to synthesize or attach specific oligonucleotides at known locations on a substrate (*see, e.g.*, page 9 of the specification). By placing specific oligonucleotides at predefined, *i.e.*, known, locations on the substrate, one, in essence, has a map of the location of each oligonucleotide which can be used to differentiate between them. In view of this ability to distinguish between the various oligonucleotides by virtue of their location on the substrate, the oligonucleotides used in the methods of the present invention are, in fact, "positionally distinguishable."

Moreover, as explained in the specification, the array used in the methods of the present invention contains oligonucleotides which will saturate all or most of the possible short subsequence recognition possibilities of the target nucleic acid and, thus, they are of varying sequences. It is pointed out, however, that although all of the possible subsequence possibilities are preferred, a less than full set of subsequences can be used (*see, e.g.*, page 21, lines 14-19 of the specification). In addition, as stated in the specification, "the oligonucleotides will preferably, but need not necessarily, be of identical length" (*see, e.g.*, page 21, lines 9-10, of the specification). As such, although it is preferred that all of the

oligonucleotides be of the same length, such is not a requirement of the methods of the present invention.

In addition, Applicants respectfully point out that the very large scale immobilized polymer synthesis technology, *i.e.*, the VLSIPS™ technology, has enabled and mechanized the preparation of the arrays used in the methods of the present invention. Thus, using the teachings of U.S. Patent No. 5,143,854, the teachings of which were incorporated into the above-referenced patent application, one of ordinary skill in the art can readily prepare a substrate having a positionally defined matrix pattern of all possible oligonucleotides of a given length. Moreover, the terminology used to describe such arrays has become standardized. In fact, the terms used by Applicants in their claims are truly terms of the art which are fully understood by those of skill in the art.

In view of the foregoing remarks, Applicants respectfully submit that the § 112, second paragraph, concerns of the Examiner have been overcome. Accordingly, Applicants urge the Examiner to withdraw this portion of the § 112, second paragraph, rejection.

b. The Examiner has raised some concern over the use of the word "substantially" in claim 2.

Applicants respectfully submit that the term substantially is not indefinite. As explained above, the array used in the methods of the present invention contains oligonucleotides which will saturate all or most of the possible short subsequence recognition possibilities of the target nucleic acid and, thus, they are of varying sequences. Moreover, although all of the possible subsequence possibilities are preferred, a less than full set of subsequences can be used. More particularly, although a substantial fraction will preferably be at least about 70%, it may be less than that (*see*, *e.g.*, page 21, lines 14-19 of the specification). Clearly, in view of these teachings, those of skilled in the art would fully understand the meaning of the term "substantially." As such, Applicants respectfully submit that claim 2, read in light of the specification, reasonably apprises those skilled in the art of the scope of the invention and, thus, the use of the word "substantially" in claim 2 does not render it indefinite or ambiguous. Accordingly, Applicants urge the Examiner to withdraw this portion of the § 112, second paragraph, rejection.

c. The Examiner has raised some concern over the use of the word "about" in claims 3 and 4.

Applicants respectfully submit that the descriptive term "about," which is used to explain the claimed ranges, does not render a claim indefinite under 35 U.S.C. § 112 (*see, e.g., W.L. Gore & Assoc., Inc. v. Garlock, Inc.*, 220 U.S.P.Q. 303 (Fed. Cir. 1983). In fact, as held by the Board of Patent Appeals in *Ex parte Eastwood*, 163 U.S.P.Q. 316, 317 (Bd.Pat.App. 1968), "about" is not broad or arbitrary, but rather is a flexible term with a meaning similar to "approximately." The Board's interpretation of "about" is consistent with the definition of "about" set forth in *Webster's II New Riverside University Dictionary*, a copy of which is provided as Exhibit A for the convenience of the Examiner. Moreover, as a matter of law, the term "about" is a "clear warning that exactitude is not claimed, but rather a contemplated variation." *See, Syntex Inc. v. Paragon Optical Inc.*, 7 U.S.P.Q.2d 1001, 1038 (D. Ariz. 1987), citing *Kolene Corp. v. Motor City Metal Treating, Inc.*, 163 U.S.P.Q. 214, 220 (E.D. Mich. 1969), *aff'd*, 169 U.S.P.Q. 77 (6th Cir. 1971), *cer't denied*, 171 U.S.P.Q. 325 (1971). As such, one of ordinary skill in the art would interpret the term "about" to have a meaning similar to "approximately" as the Board of Appeals did in *Ex parte Eastwood, supra*, and, thus, the use of the term "about" does ***not*** render claim 3 and 4 indefinite or ambiguous. Accordingly, Applicants urge the Examiner to withdraw this portion of the § 112, second paragraph, rejection.

c. The Examiner has raised some concern over the use of the word "unligatable" in step (c) of claim 17.

As noted above, step (c) of claim 17 has been amended to replace the word "unligatable" with the word "unligated." Applicants apologize for this typographical error.. In view of the amendment made to step (c) of claim 17, the Examiner's rejection is rendered moot. Accordingly, Applicants urge the Examiner to withdraw this portion of the rejection under § 112, second paragraph.

d. The Examiner has raised some concern over the fact that independent claims 1 and 17 do not contain a phrase in the last step that states the accomplishment of the goals of the claimed method.

In order to expedite prosecution of the present case, Applicants have amended claims 1 and 17 to set forth the accomplishment of the goals of the claimed method. Such goals, *i.e.*, the sequencing of a target nucleic acid, are stated in the preamble of claims 1 and 17 and, thus, no new matter is introduced. In view of the amendments made to claims 1 and 17, the Examiner's rejection is rendered moot. Accordingly, Applicants urge the Examiner to withdraw this portion of the rejection under § 112, second paragraph.

In view of the foregoing amendments and remarks, Applicants respectfully submit that the claims, read in light of the specification, reasonably apprise those skilled in the art of the scope of the invention and, thus, the claims are not indefinite or ambiguous. Accordingly, Applicants urge the Examiner to withdraw the rejection under 35 U.S.C. § 112, second paragraph.

REJECTION UNDER 35 U.S.C. § 103

It is well-settled that in considering obviousness under 35 U.S.C. § 103, the prior art as a whole must be considered and its teachings must be viewed as they would have been by one of skill in the art at the time of the invention. To properly support a rejection based upon *prima facie* obviousness, the Examiner must cite to a combination of prior art references which sets forth the necessary elements of the claimed invention ***and*** which provides the motivation for combining those elements to yield the claimed invention. *See, e.g., Northern Telecom Inc. v. Datapoint Corp.*, 15 U.S.P.Q.2d 1321, 1323 (Fed. Cir. 1990). If either the necessary elements of the invention or the motivation to combine such elements is missing, the Examiner cannot properly support the rejection based upon 35 U.S.C. § 103 and it must be withdrawn.

In response to the Examiner's *prima facie* case of obviousness, Appellants respectfully submit that the § 103 obviousness rejection of claims 1-17 is improper for four reasons. First, the combination of prior art references cited by the Examiner ***fails*** to provide a motivation for carrying out the claimed invention. Second, the Examiner has improperly used Applicants' specification as a road map through the prior art to reconstruct the claimed invention.

A. Rejection of Claims 1-16

Claims 1-16 are rejected under 35 U.S.C. § 103 as being unpatentable over Fodor, *et al.* in view of Sambrook, *et al.* Fodor, *et al.* is cited by the Examiner as reaching a method of sequencing comprising the steps: a) combining a_i) an oligonucleotide array composed of 8- to 15-mers and up to 10^6 oligonucleotides, and a_{ii}) a target nucleic acid to form hybrid complexes; and c) detecting remaining complexes bound to oligonucleotides. The Examiner acknowledges that Fodor, *et al.* teach neither Applicants' step b), *i.e.*, adding a nuclease to digest hybrid complexes which are not perfectly complementary, nor the use of specific nucleases. Based upon these two teachings, the Examiner has concluded that it would have been *prima facie* obvious to one of ordinary skill in the art to combine the sequencing method of Fodor, *et al.* with the use of nucleases to distinguish perfectly complementary hybrid complexes from imperfectly complementary complexes as taught by Maniatis. For the reasons set forth herein, Applicants ***disagree***.

1. **Fodor, *et al.* And Sambrook, *et al.* Fail To Provide The Motivation To Combine The Elements In the Manner Proposed By The Examiner**

The law is clear that an Examiner setting forth a proper *prima facie* case of obviousness must first identify the salient elements of the invention in the prior art. Once identified, the elements can only be combined if there is a suggestion in the art to combine such elements, or if the Examiner can articulate in a clear and convincing manner the reason why the invention is obvious in light of the teachings of the prior art. As the Board of Appeals stated in *Ex parte Clapp*, 227 U.S.P.Q. 972 (1985):

> Presuming arguendo that the references show the elements or concepts urged by the examiner, the examiner has presented no line of reasoning . . . as to why the artisan viewing only the collective teachings would have found it obvious to selectively pick and choose the elements and/or concepts from the several references relied on to arrive at the claimed invention . . . To support the conclusion that the claimed combination is directed to obvious subject matter, either the references must expressly or impliedly suggest the claimed combination or the Examiner must present a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references. . . . It is to be noted

> that simplicity and hindsight are not proper criteria for resolving the issue of obviousness.

See, Id. at 973 (citations omitted).

In the present case, the Examiner has concluded that an ordinary practitioner would have been motivated to combine the sequencing methods of Fodor, *et al.* with the nuclease methods of Maniatis [Sambrook, *et al.*] for the explicitly stated benefits of sensitivity, reduction of artifacts, and ease with which radiolabeled RNA probes can be synthesized (*see*, page 9 of the Office Action). Applicants ***disagree*** and, in doing so, they respectfully submit that the combination of references cited by the Examiner fails to provide the motivation necessary to combine the sequencing methods of Fodor, *et al.* with the nuclease methods of Sambrook, *et al.* in a combinatorial chemistry format.

In making the § 103 obviousness rejection, the Examiner has articulated what he perceives to be sufficient motivation to combine the sequencing methods of Fodor, *et al.* with the nuclease methods of Sambrook, *et al.*, but an analysis of the Examiner's motivation reveals that it is flawed. In support of the motivation to combine the various elements of the claimed method, the Examiner has cited to page 7.71 of Sambrook, *et al.* wherein it is stated:

> The sensitivity of this method is therefore approximately 20-fold greater than that attainable with double-stranded DNA probes or end-labeled single-stranded DNA probes and approximately equal to that attainable with uniformly labeled single-stranded DNA probes. Furthermore, the digestion of RNA:RNA hybrids with RNAse appears to suffer from fewer artifacts than digestion of RNA:DNA hybrids with nuclease S1. For these reasons and because of the relative ease with which radiolabeled RNA probes can be synthesized, it is not surprising that RNAse digestion of RNA:RNA hybrids has become a standard method ***to quantitate mRNA molecules, to map their termini, and to determine the position of introns within the corresponding gene*** (emphasis added).

Based on the foregoing, the Examiner has concluded that the claimed methods are obvious.

Applicants, however, submit that the claimed methods are not directed to quantitating mRNA molecules, mapping their termini or determining the positions of introns within the corresponding gene. In contrast to these methods, Applicants' claims are directed

to sequencing methods wherein a nuclease treatment is used following hybridization to improve the quality of hybridization signals on high density arrays and, in turn, to more accurately determine the sequence of a target nucleic acid. There is nothing about the disclosed methods of quantitating mRNA molecules, mapping their termini, *etc.* which would motivate one skilled in the art to combine the sequencing methods of Fodor, *et al.* with the nuclease methods of Sambrook, *et al.* in a combinatorial chemistry format.

Moreover, the advantages associated with the use of RNAse digestion of RNA:RNA hybrids in these methods are ***not*** pertinent or relevant to the claimed methods and, thus, they ***cannot*** be said to motivate Applicants' methods. For instance, one of the stated advantages of mapping RNA with RNAse is an approximately 20-fold increase in sensitivity, but Applicants' are using the nuclease in their methods to increase specificity, ***not*** sensitivity. In addition, neither the fact that the digestion of RNA:RNA hybrids appears to suffer fewer artifacts than digestion of RNA:DNA hybrids with nuclease S1, nor the fact that radiolabeled RNA probes can be synthesized with relative ease have any bearing on Applicants' methods. Such advantages may motivate the use of RNAse digestion of RNA:RNA hybrids as a standard method to quantitate mRNA molecules, to map their termini and to determine the positions of introns within the corresponding gene, but Applicants' methods are ***not*** directed to these uses.

In addition, the Examiner has cited to page 7.58 of Sambrook, *et al.* wherein it is stated: "DNA that has not formed duplexes is hydrolyzed with nuclease S1, whereas DNA that has hybridized to RNA is protected from digestion." Applicants respectfully submit that this statement, alone or in combination with the foregoing statements, is ***not*** tantamount to a teaching that nucleases can be used following hybridization to improve the quality of hybridization signals on high density arrays and, in turn, to more accurately determine the sequence of a target nucleic acid. At best, this statement would motivate the use of S1 nuclease to discriminate between single-stranded DNA and DNA which has hybridized to RNA, but the motivation ***stops*** there. This statement provides no teaching or suggestion that a nuclease treatment can be used following hybridization in a combinatorial chemistry format to improve the quality of hybridization signals and, in turn, to more accurately determine the sequence of a target nucleic acid. Clearly, Applicants' sequencing methods do ***not*** flow from such a statement.

In view of the foregoing, Applicants respectfully submit that the § 103 obviousness rejection is improper because rather than setting forth a convincing line of reasoning as to why the artisan would have found the claimed invention to be obvious in light of Fodor, *et al.* and Sambrook, *et al.* as is required by *Ex parte Clapp*, *supra*, the Examiner has merely articulated unfounded statements of "motivation to combine." Such unfounded statements obfuscate the fact that the Examiner's § 103 obviousness rejection is imbued with hindsight gleaned from Appellants' disclosure to reconstruct the invention. Clearly, such a rejection is impermissible (*see*, *e.g.*, *Interconnect Planning Corp. v. Feil*, 227 U.S.P.Q. 543 (Fed. Cir. 1985)). Accordingly, Applicants urge the Examiner to withdraw the rejection of claims 1-16 under 35 U.S.C. § 103.

2. The Examiner Has Improperly Used Applicants' Disclosure As A Road Map To Find The Claimed Invention Obvious

In examining a patent application under 35 U.S.C. § 103, the Examiner's job is to view the prior art in the absence of Applicants' work and to determine if the prior art teaches or suggests the claimed combination or the claimed solution to a given problem. Admittedly, it is difficult for a decision maker to cast his or her mind backwards to the time the invention was made, but both the law and fairness demand that this be done.

A number of trial courts have relied upon the Federal Circuit's dictates regarding the impermissible use of hindsight and its analogizing of hindsight to a road map. For example, in commenting on the inappropriate use of hindsight, the Eastern District of Kentucky stated:

> The trier of fact, who has the invention explained during the course of a trial, must resist the temptation to use this type of hindsight [road mapping]. Under section 103, the invention must be proven to have been obvious by the suggestions of the prior art itself, and without resort to the "road map" of the patent in suit. The Federal Circuit stated:"To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which the inventor taught is used against its teacher...one cannot pick and choose among isolated disclosures in the prior art to deprecate the claimed invention" *In re Fine*, 5 USPQ 1596, 1600 (Fed. Cir. 1988).

Following the above law, it is inappropriate and impermissible for the Examiner to first ascertain factually what Applicants did and then view the prior art in such a manner as to select from the random facts of that art those which may be modified and then utilize them to reconstruct Applicants' invention from such prior art. However, in the instant case, the Examiner has done just this. The Examiner has improperly used Applicants' specification as a road map to isolate the claimed elements from the prior art and, in addition, he has improperly used the advantages recited in the specification to fabricate a motivation for combining such elements.

The Examiner is reminded that *all* inventions, except fundamental discoveries, arise out of pre-existing prior art elements. Nothing is ever created *de novo*. In recognition of this fundamental principle governing the evolution of human knowledge, the courts have consistently held that the prior art *itself* must contain a suggestion to combine the necessary elements, or the Examiner must present clear arguments establishing a suggestion or motivation from the prior art. Any argument for a combination of prior art elements constructed *in light of an Applicants' disclosure* is impermissible, on the grounds that it is a hindsight re-creation of the Applicant's invention.

Unfortunately, in the instant case, the Examiner's argument for combining the elements of Applicants' claimed invention engages in precisely this form of impermissible hindsight. As noted above, the advantages which the Examiner believes would have motivated one of skill in the art to combine the sequencing methods of Fodor, *et al.* with the nuclease methods of Sambrook, *et al.* in a combinatorial chemistry format are ***not*** pertinent to Applicants' methods. For instance, the stated advantage of a 20-fold increase in sensitivity when mapping RNA with RNAse has nothing to do with Applicants' invention and, thus, it cannot be said that this advantage motivates the present invention. Again, Applicants' methods are concerned with specificity, ***not*** sensitivity. Similarly, neither the fact that the digestion of RNA:RNA hybrids appears to suffer fewer artifacts than digestion of RNA:DNA hybrids with nuclease S1, nor the fact that radiolabeled RNA probes can be synthesized with relative ease have any bearing on Applicants' methods. Such advantages may motivate the use of RNAse digestion of RNA:RNA hybrids as a standard method to quantitate mRNA molecules, to map their termini and to determine the positions of introns within the corresponding gene, but Applicants' methods are ***not*** directed to these uses.

In view of the foregoing, it is apparent that the Examiner has engaged in the impermissible hindsight re-creation of Applicant's invention. Accordingly, the obviousness rejection of claims 1-16 under 35 U.S.C. § 103 is improper and must be withdrawn.

B. Rejection of Claims 17 and 18

Claims 17-18 have been rejected under 35 U.S.C. § 103 as being unpatentable over Fodor in view of Keith, *et al.* (U.S. Patent No. 5,093,245). As explained above, Fodor, *et al.* is cited by the Examiner as disclosing a sequencing method. Keith, *et al.* is cited by the Examiner as disclosing the ligation of labeled oligonucleotides with T4 DNA ligase for the detection of DNA. Based upon these two teachings, the Examiner has concluded that it would have been *prima facie* obvious to one of ordinary skill in the art to combine the sequencing method of Fodor, *et al.* with the ligation methods of Keith, *et al.* For the reasons set forth herein, Applicants ***disagree***.

1. Fodor, *et al.* And Keith, *et al.* Fail To Teach or Suggest The Sequencing Method Recited In Claims 18 and 18

As explained above, the law is clear that an Examiner setting forth a proper *prima facie* case of obviousness must first identify the salient elements of the invention in the prior art. Once identified, the elements can only be combined if there is a suggestion in the art to combine such elements, or if the Examiner can articulate in a clear and convincing manner the reason why the invention is obvious in light of the teachings of the prior art. In view of these mandates, Applicants respectfully submit that the § 103 obviousness rejection of claims 17 and 18 is improper because the Examiner has failed to set forth a convincing line of reasoning as to why the claimed method is obvious in light of the prior art as is required by *Ex parte Clapp*, *supra*.

As the Examiner has noted, Fodor, *et al.* teach, *inter alia*, sequencing methods. In addition, Keith, *et al.* disclose and claim a method wherein double-stranded DNA fragments are labeled with detectable double-stranded nucleic acid that possesses a terminus complementary to at least one terminus of the double-stranded DNA fragments to be labeled. In the method of Keith, *et al.* the labeling reaction is performed using a ligase to couple the complementary ends and a restriction enzyme to produce the complementary ends

on the DNA fragment and to prevent unintended ligation of the fragments to each other. In this method, the joining of the nucleic acid labeling segment to the double-stranded DNA fragment results in loss of the restriction enzyme recognition sequence.

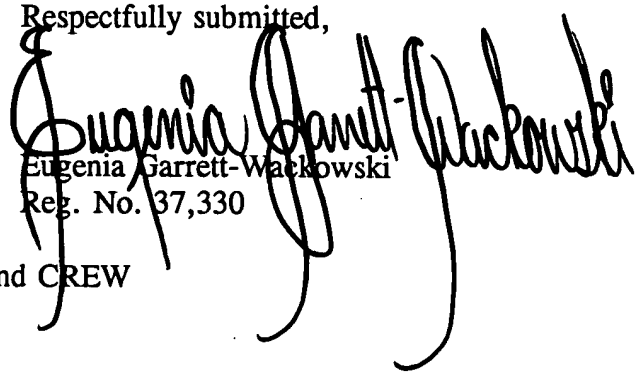
Applicants respectfully submit that the labeling method disclosed and claimed in Keith, *et al.* is fundamentally different from Applicants' sequencing method. In fact, a comparison of the method of Keith, *et al.* with Applicants' method reveals that the only point of commonality between the two methods is that they both involve the use a ligase. Beyond this point, however, the methods are totally divergent. For instance, in contrast to the method Keith, *et al.*, Applicants' method does not involve labeling double-stranded DNA fragments with detectable double-stranded nucleic acid. Moreover, in contrast to the method of Keith, *et al.*, Applicants method does not involve ligating a label onto a fragment in the presence of a restriction enzyme. In addition, in contrast to the method of Keith, *et al.*, Applicants' ligation step does not result in the loss of a restriction enzyme recognition sequence. As such, contrary to the Examiner's allegation, the method of Keith, *et al.* is not even remotely similarly Applicants' method.

In view of the significant ***differences*** between the method of Keith, *et al.* and Applicants' method, it is respectfully submitted that Fodor, *et al.* in combination with Keith, *et al.* does not render obvious the sequencing method recited in claims 17 and 18. In fact, the only way to arrive at Applicants' sequencing method based on the teachings of Fodor, *et al.* and Keith, *et al.* is to use the claimed invention as an instruction manual or "template" to pick, choose and delete pieces of the prior art so that the claimed invention is rendered obvious. However, this is hindsight re-construction of the invention which is clearly impermissible. Accordingly, the obviousness rejection of claims 17 and 18 under 35 U.S.C. § 103 is improper and must be withdrawn.

In view of the foregoing, Applicants believe all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at (415) 543-9600.

Respectfully submitted,



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